

Review of: "Methadone In Chronic Non-Oncological Pain: From Disassuefaction Of Painkillers Abuse To The Primary Management Of Opioid Hyperalgesia"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

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1. Because chronic non-oncological pain and opioid-induced hyperalgesia are important medical problems and difficult to treat the manuscript is of scientific interest.

2. It is not clear whether this manuscript is a review or an original research article. 3. The presented data on the pharmacodynamics and pharmacokinetics of methadone are correct. 4. Figure 2a shows the curve of the rise in opioid overdose deaths. One of the curves shows the mortality commonly prescribed opioids (natural and semisynthetic opioids and methadone) but lacks any indication regarding the mortality determined only by methadone. 5. Image 2b has no explanation and no source from which it is obtained (It is not clear whether the data refer to Italy or the United States). 6. For image 3 the source is not indicated. 7. There are no data on the results obtained by administering methadone in chronic pain. There are no references to the percentage of favorable therapeutic results or to cases in which methadone treatment did not work. 8. There are no comparisons between the results of methadone therapy in chronic pain and other treatments applied in this disease.

In the absence of these comparisons and statistically significant differences in favor of the results obtained by methadone administration, it is difficult to recommend the use of methadone.

9. Any data regarding the proportion of favorable results obtained by the administration of methadone in morphine hyperalgesia are missing. 10. The sentence "After all, substance abuse is present in 25-40% of patients who are hospitalized" (pg.11) is not supported by References and is not related to the subject of the article. 11. Regarding Conclusions: Because methadone was made in 1937-1939 by Gustav Ehrhart and Max Bockmühl and approved in the USA for use as an analgesic in 1947, we believe that the statement "Methadone remain a mysterious drug" after 70 years of use and research is not appropriate.

In this form the article cannot be published. The manuscript must be restructured, completed and its quality increased.